## REMARKS

Claims 1, 4-13, and 16, all of the pending claims in this application, are rejected in the Office Action dated December 14, 2007. Claim 1 has been amended to more clearly define the claimed tetrahydroquinoline derivatives of Formula I. Support for the amendments in claim 1 can be found on page 5, lines 4 to 16, and on pages 27 to 56 (examples 1 to 50) of the specification. Applicants respectfully request entry of the above amendments and reconsideration of the claims.

Claims are Non-obvious

Claims 1 and 4-13 are rejected under 35 U.S.C. §103(a) as being allegedly obvious over Van Straten et al. (PCT Int. Appl. WO 20030004028) or Van Straten et al. (US 2004/0236109). According to the Examiner the references constitute prior art only under 35 U.S.C. §102(e). The Examiner asserts that the claimed compounds are analogs of old compounds and therefore obvious to one of ordinary skill in the art with the expectation to have similar properties.

In response Applicants submit that subject matter in the cited references, which constitute prior art only under 35 U.S.C. §102(e), and the currently claimed subject matter were commonly owned and under obligation to be assigned to the same person at the time the invention herein was made. Therefore, the cited references do not constitute prior art for purposes of obviousness as under 35 U.S.C §103(c). Accordingly, Applicants respectfully request withdrawal of the rejection of claims 1, and 4-13 under 35 U.S.C. §103(a).

Claims are Enabled.

Claims 1 and 4-13 are rejected under 35 U.S.C. §112, first paragraph, because, according to the Examiner, the specification, while enabling for certain compounds, does not reasonably provide enablement for the protracted list of compounds claimed. The Examiner asserts that the claims are very broad encompassing a variety of heterocycles

(mainly R4 and R5), bearing multiple substitutions as set forth on pages 2-4 and 12-15 of the Office Action and as previously asserted. The Examiner maintains the rejection because the directions for the preparation and function of all the scope of "heteroaryl" moiety is not enabled. According to the Examiner a few examples of "heteroaryl" does not enable all "heteroaryl" or "heterocyclic" on R6 and R5 (which is nested to R7, which is in turn nested to R8 and R9). Further, and as previously asserted, the Examiner maintains that while a vast array of anilines are commercially available for the Skraup reaction, the substituents R4 and R5 apparently have enormous permutations. According to the Examiner, the Skraup reaction has been known to be sensitive to substituents on the starting aniline. In addition, the Examiner asserts that the requirement for activity at the FSH receptor provides no further guidance. According to the Examiner the only available information regarding the claimed compounds is that these can be an agonist, antagonist or both for the FSH receptor. Further, a single compound cannot be both an agonist and an antagonist according to the Examiner. Moreover, in view of Van Straten et al.; Journal of Medicinal Chemistry 2005, 48, 1697-1700, stating that "aromatic substituents in position 6 (R6) are preferred . . ." and "space is limited because introduction of an extra t-butyl group in 11 led to a drop in potency" the Examiner asserts that there is an apparent size constraint on substituents. According to the Examiner, one could not make/use the claimed invention.

In response Applicants submit that for each of the possible substituents for R4 and R5 of the claimed tetrahydroquinoline derivatives of formula I at least one representative example is provided in the currently pending application. The claimed tetrahydroquinoline derivatives of formula I in independent claim 1 are clearly supported by the examples in the specification. Each one example provides a method of preparing the claimed tetrahydroquinoline derivative. Moreover, the specification on pages 9-20 provides a detailed description of methods for preparing the claimed tetrahydroquinoline derivatives of formula I. In addition, the specification provides in Example 51 methods of determining the activity (whether it be as an agonist or antagonist) for each of the disclosed examples. In fact, the specification on page 57 describes that "compounds of

all examples exhibited an $EC_{50}(IC_{50})$ value of less than $10^{-5}$M in either an agonistic or antagonistic assay set-up or both. The compounds of examples 5-8, 10-14, 16, 18-20, 33-35, 37, 38,41, and 45-50 showed an $EC_{50}$ of less than $10^{-7}$M in at least one of the assays." As described, activity (with respect to the FSH receptor) of compounds of formula I was measured with a cAMP responsive element/promoter directing the expression of a reporter gene (luciferase), binding of a ligand (compound) to the FSH receptor will result in an increase (for an agonist) of cAMP and therefore increased expression of the reporter gene. Thus, this description in Example 51 clearly describes determining agonistic properties of the claimed compounds, the description of another assay describes testing their antagonistic properties. Moreover, in the declaration by Cornelis Marius Timmers (the "Timmers declaration") submitted herewith the agonist/antagonist data for each of the examples described in the application are shown in Table 1. The data in Table 1, as it appears in the Timmers declaration, were obtained when the claimed invention was made and provided the basis for the statement in Example 51 with respect to the agonist/antagonist activity without actually including the table itself in the specification of the current application.

In addition, with respect to the Examiner's statement that some compounds show both agonist and antagonist activity, Applicants submit that some of the claimed compounds, as indicated in the specification and demonstrated in the table in the Timmers declaration, indeed show both agonist and antagonist activity in the assays described in Example 51 of the specification. Applicants thus submit that some compounds can interact with the FSH-receptor and have both agonist and antagonist activity. The Examiner has provided no evidence to question this experimental evidence discussed in the currently pending application. In addition, the Timmers declaration provides the explanation that some compounds may have both agonistic and antagonistic activity as a function of their concentration. Therefore, the observation that some of the claimed tetrahydroquinoline derivatives are both agonist and antagonist is not a contradiction as suggested by the Examiner's comments, which comments are unfounded and contrary to the observed experimental results.

Thus, Applicants submit that the specification provides an enabling disclosure for the claimed tetrahydroquinoline derivatives of formula I describing at least one synthetic method for such derivative as well as showing activity with respect to the FSH receptor. For these reasons Applicants submit that the skilled artisan reading the disclosure of the currently pending application would know how to make and/or use the claimed invention. Accordingly, Applicants submit that claims 1, and 4-13 are clearly enabled by the specification as filed and respectfully request withdrawal of the rejection of claims 1, and 4-13 under 35 U.S.C. §112, first paragraph.

Claim 16 is rejected under 35 U.S.C. §112, first paragraph for failing to comply with the enablement requirement. The Examiner asserts that while the claim is directed to a method of fertility regulation there is no nexus between the claimed compounds and methods of fertility regulation as set forth on pages 5-6 and 15-16 of the Office Action and as previously asserted. The Examiner maintains the rejection because the paucity of data in the specification, the relatively poorly developed understanding of the effect of FSH receptor agonists/antagonists, and the myriad of different physiological functions encompassed by the term "fertility regulation" clearly warrant the conclusion of lack of enablement. Further, and as previously asserted by the Examiner the FSH receptor, a G-protein coupled receptor with a vast number of binding sites and conformations, may be associated with distinct physiological outcomes depending on the binding site that is activated. In view of this statement the Examiner refers to Guo, Tao; Expert Opinion on Therapeutic Patents 2005, 15(11), 1555-1564, stating that only in the clinic will the question of whether a small molecule FSH receptor modulators will be successful as fertility agents be answered. According to the Examiner there is no successful use of the compounds in the claimed method in an animal model and no clear correlation between antagonism of this receptor and a therapeutic outcome. The Examiner also refers to a passage in the Kenakin et al. article, "The ligand paradox between affinity and efficacy: can you be there and not make a difference", TRENDS in Pharmacological Sciences, 2002, 23, 275-280", to allegedly show that in the present case

"we have exactly this situation, namely a ligand with affinity, but not known function, which as Kenakin et al. concluded ". . .the discovery of macro-affinity of a ligand for a receptor should be considered only a starting point for the optimal exploitation of a drug for therapeutic utility."

In response, Applicants submit that the claimed tetrahydroquinoline derivates of formula I are shown to be ligands (either as agonist or antagonist) for the FSH receptor, as demonstrated in Example 51 of the specification of the currently pending application and in Table 1 of the Timmers declaration. With respect to some compounds showing both agonistic as well as antagonistic activity, the Timmers declaration provides the explanation that some compounds may have both agonistic and antagonistic activity as a function of their concentration. The assay determining efficacy of the claimed tetrahydroquinoline derivatives as either an agonist or antagonist for the FSH receptor relies on cAMP accumulation as described in Example 51 and further on page 22, line 11 to page 23, line 6 of the specification. Activation of the FSH receptor with FSH has previously been correlated with cAMP accumulation. Further, FSH receptor activation with FSH is a well described pathway in regulating fertility. Thus, applicants submit there is a clear nexus between the observed activity of the claimed tetrahydroquinoline derivatives of formula I and a method of regulating fertility.

In addition, Applicants reiterate that as previously submitted the Examiner's statement citing Tao Guo is taken out of context. Guo does not dispute that activation or inhibition of the FSH receptor by small molecules, to which class of compounds the claimed tetrahydroquinoline derivatives of formula I belong and which have been shown to have acceptable agonist and/or antagonist activity, as demostrated in the Timmers declaration, provides no nexus with respect to regulating fertility. Indeed, Guo indicates a correlation between antagonism of the FSH receptor and a therapeutic outcome, i.e., fertility regulation. In this regard, the Examiner's attention is directed to Guo, page 1562, second column, wherein it states inter *alia:*

> "Most importantly, FSHR antagonists, such as compounds 24 and 25, have been demonstrated to inhibit oestradiol synthesis and ovulation in female rats [62-64], bolstering confidence that small molecule FSHR antagonist could be developed into novel, non-steroidal contraceptives in women..."

Accordingly, in contrast to the Examiner's statement that "[T]here is no successful use of these compounds in an animal model and no clear correlation between antagonism of this receptor and a therapeutic outcome, thus undue experimentation would be required", Guo indicates that compounds functioning as FSHR antagonists have been shown in animals to possess therapeutic utility. The statement by Guo that "only in the clinic will the question of whether small molecule LHR and FSH modulators will be successful as fertility-regulating agents be answered," is directed to the commercial development of one or a few of such small molecules which may actually be used in the treatment of patients. However, a variety of factors not necessarily related to efficacy or ability to modulate fertility by such compound are considered in order to arrive at such [commercially] successful small molecule. In other words considerations such as for example lowest degree of potential side effects or the level of cross reactivity may be additional factors that are considered.

Applicants submit that these considerations are unrelated as to whether or not the claimed tetrahydroquinoline derivative of formula I can be used to regulate fertility. With respect to the Examiner's statement pertaining to the Kekankin et al. article, the fact remains that while Kenakin et al. discuss in general that ligands will produce a bias in the conformation of the receptor ensemble, Kenakin et al., in the passage cited by the Examiner, states nothing whatsoever regarding the therapeutic utility of FSH antagonists, in particular, the presently claimed compounds. As stated above, Guo clearly indicates a correlation between antagonism of the FSH receptor by compounds functioning as FSH antagonists and a therapeutic outcome. Furthermore, the Timmers declaration clearly provides the experimental data, obtained prior to the time the application was filed, for either such agonist activity, antagonist activity, or both.

For all of the above reasons, Applicants submit there is a nexus between the claimed compounds and methods of fertility regulation as in claim 16. Accordingly, Applicants submit that claim 16 is clearly enabled by the specification as filed and respectfully request withdrawal of the rejection of claim 16 under 35 U.S.C. § 112, first paragraph.

Double Patenting Rejection.

Claims 1, 4-13, and 16 are provisionally rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 1-9 of copending application 10/482,707 and over claims 1-9 of copending application 10/540,335. According to the Examiner, although the wording of these allegedly conflicting claims is not identical they are not patentably distinct because there is substantial overlap in scope of the claims. The Examiner notes that the wording is only slightly different and that the '707 application is broader and the '335 application is narrower.

In response to the obviousness-type double patenting rejection of claims 1, 4-13, and 16 over claims 1-9 of co-pending application 10/482,707 ("the '707 application"), Applicants submit, as previously argued, that the claimed tetrahydroquinoline derivatives of formula I are very different from the compounds in claims 1-9 of the co-pending '707 application. In the currently claimed invention the tetrahydroquinoline derivatives of formula I require that **both** positions 5 and 7 of the benzene ring of the bicyclic tetrahydroquinoline are substituted with R4 and R5 respectively, whereas the compounds in the '707 only require **one** substituent on any one of positions 5, 7 and 8 of the same benzene ring. If however one of these substituents in the claimed invention is hydrogen, R4 may be H, the other substituent (R5) is selected from amino, (di)(1-4C)alkylamino, (2-5C)heteroarylcarbonylamino, (2-5C)heteroarylcarbonyloxy, $R^8$-(2-4) alkoxy, $R^9$-methylamino or R9-methoxy, all of which differ substantially from the possible substituents disclosed in the '707 application for this position. There is no teaching or suggestion in the '707 application that the 5, 7, and 8 positions of the benzene ring of the

tetrahydroquinoline compound disclosed therein can be substituted as in the claimed invention. Accordingly, Applicants submit that, in contrast to the Examiner's assertions, there is no overlap between the claimed compounds and that the compounds in claims 1-9 of the co-pending '707 application nor does the disclosure in the '707 application teach or suggest the claimed tetrahydroquinoline derivatives. For this reason Applicants respectfully request withdrawal of the provisional rejection of claims 1, 4-13 and 16 under the non-statutory doctrine of obviousness type double patenting.

In response to the obviousness-type double patenting rejection of claims 1, 4-13, and 16 over claims 1-9 of co-pending application 10/540,335, Applicants defer responding to the rejection until such time as any of the above claims are allowed at whichtime Applicants, although disagreeing with the Examiner's assertions, intend to submit aproper Terminal Disclaimer.

In view of the above amendment, Applicants believe the pending application is in condition for allowance. If the Examiner believes a telephone conference would be of value, he is requested to call the undersigned at the number listed below. Applicants respectfully request the issuance of a timely Notice of Allowance in the case.

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Respectfully submitted,

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